Original Article

The implementation of the guideline for the management of pediatric off-label use of drugs in China: a cross-sectional study

Min Meng[1,2,3,4#], Jiale Hu[5#], Wenjuan Lei[4], Min Tian[4], Xiao Liu[6], Yali Lu[4], Enmei Liu[2,3], Shu Zhang[2,3], Zhu Han[7], Qiu Li[2,3,8], Yaolong Chen[1,2,3,9,10,11]

[1]Chevidence Lab of Child & Adolescent Health, Children's Hospital of Chongqing Medical University, Chongqing, China; [2]National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China; [3]Chongqing Key Laboratory of Pediatrics, Chongqing, China; [4]Department of Pharmacy, Gansu Provincial Hospital, Lanzhou, China; [5]Department of Nurse Anesthesia, Virginia Commonwealth University, Richmond, VA, USA; [6]School of Public Health, Lanzhou University, Lanzhou, China; [7]College of Pharmacy, Gansu University of Chinese Medicine, Lanzhou, China; [8]Department of Nephrology, Children's Hospital of Chongqing Medical University, Chongqing, China; [9]Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical Sciences (2021RU017), School of Basic Medical Sciences, Lanzhou University, Lanzhou, China; [10]WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, Lanzhou, China; [11]Lanzhou University GRADE Center, Lanzhou, China

Contributions: (I) Conception and design: M Meng, J Hu; (II) Administrative support: Q Li, Y Chen; (III) Provision of study materials or patients: E Liu, S Zhang; (IV) Collection and assembly of data: Y Lu, Z Han; (V) Data analysis and interpretation: W Lei, M Tian, X Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yaolong Chen, MD, PhD. Chevidence Lab Child & Adolescent Health Department, Children's Hospital of Chongqing Medical University, 136 Zhongshan Second Street, Chongqing 400014, China; National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China; Chongqing Key Laboratory of Pediatrics, Chongqing, China; Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical Sciences (2021RU017), School of Basic Medical Sciences, Lanzhou University, Lanzhou, China; WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, Lanzhou, China; Lanzhou University GRADE Center, Lanzhou, China. Email: chenyaolong@lzu.edu.cn; Qiu Li, MD, PhD. Department of Nephrology, Children's Hospital of Chongqing Medical University, 136 Zhongshan Second Street, Chongqing 400014, China; National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing, China; Chongqing Key Laboratory of Pediatrics, Chongqing, China. Email: liqiu809@hospital.cqmu.edu.cn.

Background: Previously, we developed the Guidelines for the Management of Pediatric Off-Label Use of Drugs in China in addressing the need for standardization of pediatric off-label drug use. As the implementation of recommendations in Guidelines among healthcare professionals is weak, it is important to identify barriers to guideline implementation for developing appropriate strategies for specific settings and target groups. This study aimed to assess the difficulty and urgency in implementing the recommendations in the Guideline, identifying the factors affecting the implementation of these recommendations to realize the clinical translation of the Guideline.

Methods: A cross-sectional study was conducted from March 1 to June 17, 2022. Pediatricians, pharmacists, and health managers from all 31 mainland Chinese provinces were involved. The electronic questionnaires were distributed nationwide by The Clinical Pharmacology Group of the Pediatric Society of the Chinese Medical Association and the National Clinical Research Center for Child Health. Data analysis, including frequency, percentages, averages, and standard deviations was performed using Microsoft Excel 16.54. Chi-squared tests, multi-factor logistic regression, and linear regression were analyzed in SPSS 23.0. A Sankey diagram was constructed using R software.

Results: A total of 869 valid questionnaires were collected from 491 participating organizations. More than half of the recommendations were implemented, and 12 recommendations were implemented more in

tertiary hospitals than in secondary hospitals. The mean urgency scores of all 21 recommendations were over 5. The mean difficulty scores of all 21 recommendations were over 4. The percentage of the most urgent was 44.33%, and the least urgent was 1.45%. The most difficult portion was 12.03%, and the least difficult was 5.74%. Factors impacting the urgency and difficulty of guideline implementation were different, with common influences including the position, education level of clinicians and hospital level.

Conclusions: The recommendations in the Guideline for the Management of Pediatric Off-Label Use of Drugs are considered highly urgent for implementation in China. Nevertheless, the study revealed challenges in applying all 21 recommendations within clinical practice. The key factors affecting implementation include the position, education, experience, and hospital level of healthcare professionals. It is recommended to facilitate implementing the recommendations by sharing experience across various hospital levels, starting from high-level hospitals and extending to primary healthcare settings. Moreover, adjustments to the professional structure within hospitals are needed to enhance the management of off-label drug use in pediatric patients.

Keywords: Pediatric; cross-sectional studies; off-label use; questionnaires; China

Submitted May 21, 2024. Accepted for publication Aug 19, 2024. Published online Aug 28, 2024.
doi: 10.21037/tp-24-198
View this article at: https://dx.doi.org/10.21037/tp-24-198

Introduction

Off-label drug use in pediatrics is a global public health issue (1), with studies indicating that the prevalence of off-label drug use ranges from 3.2% to 95% in pediatrics and from 26% to 95% in infants (2,3). According to a systematic review, pediatric off-label prescription rates ranged from 22.7% to 51.2% in outpatient settings and 40.48% to 78.96% in hospitalized children in China (4). In our previous cross-sectional study of pediatric outpatient prescriptions in Gansu Province, 38.0% involved off-label use (5). The highest rate of off-label drug use in outpatient children's prescriptions was 90.0% in a single-center study of antidepressant prescriptions in China (6). Therefore, developing evidence-based recommendations on the off-label use of drugs in pediatrics in China is crucial.

The Chinese Society of Pediatric Clinical Pharmacology, in conjunction with the Chinese Medical Association, has jointly published "the Expert Consensus on Off-label Drugs in Pediatrics in China" (7). Over the past 5 years, in tandem with the emergence of new evidence, the standards, guidelines, and consensus statements pertaining to the off-label use of drugs in pediatrics have undergone significant updates. Despite the global progress in addressing pediatric off-label drug use, a notable gap remains in China, where an updated consensus statement or guideline specific to this issue is yet to be established. This absence highlights a critical need for clinicians and policymakers to collaborate in developing evidence-based guildines that reflect the unique characteristics and needs of Chinese pediatric population. To address the need for standardized pediatric off-label drug use in China, the Chinese Society of Pediatric Clinical Pharmacology, alongside the Chinese Medical Association and the National Clinical Research Center

Highlight box

Key findings

- The implementer and the context affect the Guidelines for the Management of Pediatric Off-Label Use of Drugs in China. We clarified the facilitators and barriers to its implementation.

What is known and what is new?

- Identifying research gaps contributes to health practice and policy implementation, and guideline developers should be proactive in identifying research gaps and suggesting ways to address them to facilitate clinical practice translation.
- The recommendations in the Guideline for the Management of Pediatric Off-Label Use of Drugs have high urgency of implementation in China. The key factors influencing implementation were the position, education, experience, and hospital level of healthcare professionals.

What is the implication, and what should change now?

- It is suggested that guideline developers should design further tailored implementation strategies based on the contextual factors influencing pediatric off-label drug use.

for Child Health and Disorders, have partnered with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Center in China, developed the "Guideline for the Management of Pediatric Off-label Use of Drugs in China" (i.e., the Guideline) (Appendix 1) (8). This guideline consolidates the latest evidence to provide healthcare professionals with a clear framework for safely and effectively managing off-label drug use in pediatric, reflecting a significant step forward in pediatric healthcare in China.

Numerous studies have demonstrated that up to 70% of clinicians across most fields and nations fail to adhere to Clinical Practice Guidelines (CPGs) (9,10). According to studies in China, the implementation of evidence-based recommendations in CPGs among medical staff is even worse, around 50% (11). To the Expert Consensus on Off-label Drugs in Pediatrics in China, a study by Mei *et al.* concluded that using off-label drugs in pediatrics was common in Shanghai, but more than half of the respondents declared that they did not adhere to the process proposed in the consensus (12). Clinician attitudes, discrepancies between patient preferences and CPGs, and CPGs dissemination may affect guidelines' adherence (13). Identifying research gaps contributes to health practice and policy implementation (14), and guideline developers should be proactive in identifying research gaps and suggesting ways to address them to facilitate clinical practice translation (15). Thus, guideline implementation and compliance barriers must be identified in advance to develop appropriate strategies for specific settings and target groups (16). To create strategies to promote evidence utilization, analyzing the facilitators and barriers to managing off-label drug use in children is required (17). Thus, this study aims to use a cross-sectional study to determine the degree of difficulty and urgency in implementing each recommendation of the Guideline, and identify factors impacting gaps, urgencies, and difficulties. We present this article in accordance with the SURGE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-198/rc).

Methods

Study design

A cross-sectional study using the survey method was conducted from March 1 to June 17, 2022.

Participants and setting

The study was pre-tested by 48 healthcare professionals, including pediatricians, pharmacists, nurses, and health administrators. However, according to the pre-test findings, nurses did not feel involved in implementing the Guideline's recommendations. They had no experience with the survey items. As a result, the respondents in this study only included pediatricians, pharmacists, and health administrators from regionally representative secondary and tertiary hospitals in 31 provinces of Mainland China. The study adopted the principle of convenience sampling.

At a confidence level of 99% and a sampling error of 5%, a minimum sample of 666 is required. For failure and refusal rates, another 15% were added to the sample, so that a minimum sample of 766 was required to ensure the credibility of this study. We sent out a total of 920 questionnaires covering almost every province in China, selecting representative secondary and tertiary hospitals.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Gansu Provincial Hospital (No. 2022-152). All participants provided informed consent to participate in the study.

Questionnaire

The questionnaire included three sections. The first section included 13 demographic questions for respondents, such as gender, age, workplace, etc. The second section was developed based on the 21 recommendations in the Guideline. There were three types of questions for each recommendation: (I) whether it had been implemented or not (yes or no), (II) the urgency of implementation (using a 1-7 Likert scale with a gradual increase in the urgency), and (III) the difficulty of implementation (using a 1-7 Likert scale with a gradual increase in the difficulty). The last section was an open-ended question seeking comments on implementing the Guideline (Appendix 2).

Content validation and pre-test were conducted to determine the content of the questionnaire. Three pharmacologists, a clinical expert, a health statistics expert, and a health administration expert were requested to conduct a content validity test of the questionnaire.-The second section's content validity index (I-CVI) was 0.83–1.00. A pre-test of 48 healthcare professionals showed that the questionnaire was easy to comprehend, the questions

were well phrased, and each questionnaire took between 15 and 25 minutes to complete.

Data collection

The electronic version of the questionnaires was disseminated nationally through affiliations of the Clinical Pharmacology Group of the Pediatric Society of the Chinese Medical Association and the National Clinical Research Center for Child Health. Completed questionnaires were collected manually and turned into an Excel file by the researchers. Two researchers independently validated the correctness of the completed questionnaire data to assure data quality. They reviewed all that were inconsistent with each other or with the facts. Then we excluded questionnaires in which any question was unanswered.

Statistical analysis

Descriptive data analysis was performed for the characteristics of the participating health professionals and the comments on the implementation. The descriptive analysis was calculated using Microsoft Excel 16.54, including the frequency, percentage, means, and standard deviations.

A chi-squared test was performed to determine the difference in the number of implementations of off-label drug use management between secondary and tertiary hospitals and between children's hospitals and other types of hospitals, respectively. The effect of urgency and difficulty on recommendation implementation was studied using binary logistic regression. As scores (1–7 Likert scale) were regarded as continuous variables, linear regression was used for multivariate analysis, and the stepwise regression technique was used to screen the variables. Regional distribution, hospital level, hospital type, rater's age group, degree, professional role, work experience, position, and management experience were included as the multivariate variables. Chi-squared analysis, multi-factor logistic regression, and linear regression were analyzed using SPSS 23.0. P values of 0.05 were regarded as statistically significant.

Likert scale scores for urgency and difficulty of recommendation were analyzed using means and standard deviations and were then ranked based on the values of means from most to least.

The Sankey diagram visualizes the flow of participants' choices for each recommendation (18,19). For clarity, all cumulative statistics were labeled on the cumulative bars. In this study, the left and right flows came from the central cumulative bar, with the left column indicating difficulty scores and the right column showing urgency scores. Suppose a participant is selected to implement a recommendation, its urgency (right column) and difficulty (left column) scores are streamed from the "yes" column in the middle. Thus, we can see the cumulative flow of 18,249 selections and the proportion (869 participants × 21 recommendations =18,249). R software (version 1.3.1056) was used to develop Sankey.

Results

Characteristics of the participating health professionals

A total of 895 questionnaires were collected from 491 participating organizations across 31 provinces in mainland China. Eight hundred sixty-nine questionnaires were included after 26 invalid questionnaires were excluded. The response rate was 97.1%. The essential characteristics of the included health professionals are shown as in *Table 1*, and the demographic characteristics of the secondary and tertiary hospitals as Table S1.

Most participants were female (n=610, 70.2%), had the age of 30–39 years old (n=372, 42.8%), had a bachelor's degree (n=463, 53.3%), had over 20 years of work experience (n=273, 31.4%), and had a senior position (n=360, 41.4%). The participating health professionals included 407 pediatricians (46.8%), 43 non-pediatrician clinicians (4.9%), 200 clinical pharmacists (23.0%), 163 non-clinical pharmacists (18.8%), and 56 health managers (6.4%). Six hundred thirty-one participants (72.6%) were from tertiary hospitals, and 238 (27.4%) were from secondary hospitals.

The current state of off-label drug use management in children

The top 5 recommendations were 8.2, 5.1, 1.2, 8.1, and 7.3. The percentage of all recommendations carried out ranged between 65.5% and 41.1%. More than half of the recommendations (57.14%, 12/21) had been implemented in China. The implementation of recommendations 1.1, 1.2, 2.1, 2.5, 3.2, 5.1, 7.1, 8.2, 2.2, 3.1, 4.2, and 8.1 in tertiary hospitals were conducted more than those in secondary hospitals. Except for recommendations 5.2, 6.2, 7.2, 7.3, 8.1, and 8.3, the other 15 recommendations were carried

Table 1 Characteristics of the participating health professional

Characteristics	Number	Percentage (%)
Gender		
Male	259	29.8
Female	610	70.2
Age		
20–29 years	93	10.7
30–39 years	372	42.8
40–49 years	248	28.5
50–59 years	145	16.7
≥60 years	11	1.3
Degree		
Below bachelor	72	8.3
Bachelor	463	53.3
Master	230	26.5
Doctor	104	12.0
Professional role		
Pediatrician	407	46.8
Non-pediatrician	43	4.9
Clinical pharmacist	200	23.0
Non-clinical pharmacist	163	18.8
Health manager	56	6.4
Work experience		
5 years and below	115	13.2
6–10 years	199	22.9
11–15 years	196	22.6
16–20 years	86	9.9
20 years +	273	31.4
Position[†]		
Not obtained	38	4.4
Junior	185	21.3
Intermediate	286	32.9
Senior	360	41.4
Hospital level		
Secondary	238	27.4
Tertiary	631	72.6
Hospital type		
Children's hospital	116	13.3
Others[‡]	753	86.7
Management experience		
Yes	336	38.7
No	533	61.3
Region distribution		
North China	86	9.9
Northeast China	44	5.1
East China	115	13.2
Central and south China	126	14.5
Southwest China	93	10.7
Northwest China	405	46.6
Total	869	100

[†], health worker in China is often classified as "senior", "intermediate" or "junior" position according to their skill levels and specialization; [‡], other types of hospitals, including general hospitals and other specialized hospitals with pediatric clinics.

out much more in pediatric hospitals than in other types of hospitals. The guideline recommendations are shown in Appendix 1 and the management details have been presented in Table S2.

The urgency and difficulty of guideline implementation

The mean of urgency and difficulty scores were just of slight differences between the recommendations, respectively. Almost all of the 21 recommendations received difficulty scores above 4, and all 21 recommendations received urgency scores above 5. The mean of urgency and difficulty scores for recommendations 5.2 and 5.1 were the lowest, with a mean of 5.67 and 3.93, respectively. The top five recommendations for overall urgency are 1.1, 1.2, 6.1, 4.2, and 6.2. The top five recommendations for overall difficulty are 2.3, 6.2, 6.1, 4.1, and 3.2; the mean scores of 21 recommendations were over 4. Table S3 shows the scores and rankings (see Appendix 1 for the guideline recommendations).

The association of actual recommendation implementation with the urgency and difficulty of implementation

For recommendations 1.1, 5.2, 6.1, 7.3, 8.1, and 8.2, there were significant correlations between the Likert scale scores for implementation urgency and the actual recommendation implementation (see Appendix 1 for the guideline recommendations). For all recommendations, there were significant correlations between the Likert scale scores for implementation difficulty and the actual recommendation implementation. Raters who had not implemented recommendations scored higher difficulty scores than those who had implemented them. The details are shown in *Table 2*.

Figure 1 is a Sankey diagram describing participants for each recommendation who had recommendation implementation or did not (middle column: yes or no) and how to evaluate the implementation's urgency (right column) and difficulty (left column). The total number of implemented recommendations was 9,474, with 8,775 being unimplemented. The urgent Likert scale values were 8,090 at 7, 4,057 at 6, 3,043 at 5, 2,117 at 4, 446 at 3, 265 at 1, and 231 at 2. The percentage of the most urgent was 44.33% (8,090/18,249), and the least urgent was 1.45% (265/18,249). The difficulty Likert scale values were 5,020 at 4, 3,982 at 5, 2,436 at 6, 2,196 at 7, 1,788 at 3, 1,420 at 2, and 1,047 at 1. The percentage of the most difficult was 12.03% (2,196/18,249), and the least difficult was 5.74% (14,075/18,249). 27.51% (5,020/18,249) of respondents believed the guideline's implementation was generally difficult.

Multi-factor analysis of the urgency and difficulty of guideline implementation

Factors impacting the urgency and difficulty of guideline implementation were different, but the common influencing factors included the position and education level of clinicians and hospital level. The position was positively associated with the urgency and difficulty of guideline implementation. In contrast, the education

Table 2 Logistic regression analysis of actual recommendation implementation with the urgency and difficulty of implementation

Number of recommendations	Likert scale score	B	Wald	P	OR	95% CI
Theme 1. General principles and characteristics of pediatric off-label use of drugs management						
1.1 Management principles	Urgency	−0.164	10.038	0.002	0.849	0.767–0.939
	Difficulty	0.178	15.320	<0.001	1.195	1.093–1.306
1.2 Refer to guidelines	Urgency	−0.104	3.236	0.07	0.901	0.805–1.009
	Difficulty	0.279	31.704	<0.001	1.322	1.200–1.457
Theme 2. The establishment of an expert committee on the pediatric off-label use of drugs						
2.1 Expert committee	Urgency	−0.067	1.794	0.18	0.935	0.848–1.032
	Difficulty	0.231	27.385	<0.001	1.260	1.156–1.374
2.2 Co-chair	Urgency	0.021	0.157	0.69	1.021	0.921–1.131
	Difficulty	0.177	17.478	<0.001	1.194	1.099–1.297
2.3 Expand experts	Urgency	−0.071	1.832	0.18	0.932	0.841–1.032
	Difficulty	0.323	48.831	<0.001	1.381	1.261–1.512
2.4 Drug combination	Urgency	−0.012	0.047	0.83	0.988	0.889–1.099
	Difficulty	0.335	53.646	<0.001	1.397	1.278–1.528
2.5 Responsibilities and obligations	Urgency	0.064	1.335	0.25	1.066	0.956–1.189
	Difficulty	0.345	55.105	<0.001	1.412	1.289–1.546

Table 2 (*continued*)

Table 2 (*continued*)

Number of recommendations	Likert scale score	B	Wald	P	OR	95% CI
Theme 3. Evidence evaluation of off-label drug use for children						
3.1 Recommendations follow guidelines	Urgency	0.052	0.915	0.34	1.053	0.947–1.171
	Difficulty	0.282	39.756	<0.001	1.325	1.214–1.447
3.2 Evaluate recommendations	Urgency	−0.043	0.647	0.42	0.958	0.863–1.063
	Difficulty	0.304	44.442	<0.001	1.355	1.239–1.481
Theme 4. Benefit and risk assessment of off-label drug uses in children: steps and precautions						
4.1 BRAvO decision-making framework	Urgency	0.314	0.156	0.69	1.021	0.920–1.134
	Difficulty	0.021	47.424	<0.001	1.368	1.252–1.496
4.2 Age difference	Urgency	−0.085	2.347	0.13	0.918	0.823–1.024
	Difficulty	0.381	63.516	<0.001	1.463	1.332–1.607
Theme 5. Informed consent for the off-label use of drugs in children						
5.1 Informed consent under 8 years old	Urgency	−0.057	1.077	0.30	0.945	0.849–1.052
	Difficulty	0.316	53.815	<0.001	1.371	1.260–1.492
5.2 Informed consent over 8 years old	Urgency	−0.104	4.554	0.03	0.901	0.818–0.992
	Difficulty	0.330	59.576	<0.001	1.391	1.279–1.512
Theme 6. Evidence-based practice for the off-label use of drugs in children						
6.1 Evidence-based medicine database	Urgency	0.121	4.688	0.03	1.128	1.012–1.259
	Difficulty	0.322	48.889	<0.001	1.381	1.261–1.511
6.2 Electronic medical record system	Urgency	0.083	2.240	0.13	1.087	0.975–1.212
	Difficulty	0.349	58.993	<0.001	1.418	1.297–1.550
Theme 7. Monitoring and assessment of the risk of pediatric off-label use of drugs						
7.1 Adverse reactions monitor	Urgency	−0.078	2.144	0.14	0.925	0.833–1.027
	Difficulty	0.386	67.487	<0.001	1.471	1.342–1.613
7.2 Construct ADR monitoring system	Urgency	−0.015	0.072	0.79	0.985	0.885–1.097
	Difficulty	0.438	87.119	<0.001	1.549	1.413–1.698
7.3 Cooperative monitoring	Urgency	−0.146	7.199	0.007	0.865	0.777–0.962
	Difficulty	0.369	60.441	<0.001	1.446	1.318–1.587
Theme 8. Patient education on the pediatric off-label use of drugs						
8.1 Drug education	Urgency	−0.110	3.957	0.047	0.896	0.805–0.998
	Difficulty	0.410	71.350	<0.001	1.507	1.370–1.658
8.2 Drug information list	Urgency	−0.115	4.067	0.04	0.892	0.797–0.997
	Difficulty	0.389	62.336	<0.001	1.475	1.340–1.625
8.3 Popularized material	Urgency	−0.017	60.693	0.75	0.983	0.884–1.093
	Difficulty	0.358	0.101	<0.001	1.430	1.307–1.565

OR, odds ratio; CI, confidence interval; BRAvO, Benefit and Risk Assessment for Off-label Use.

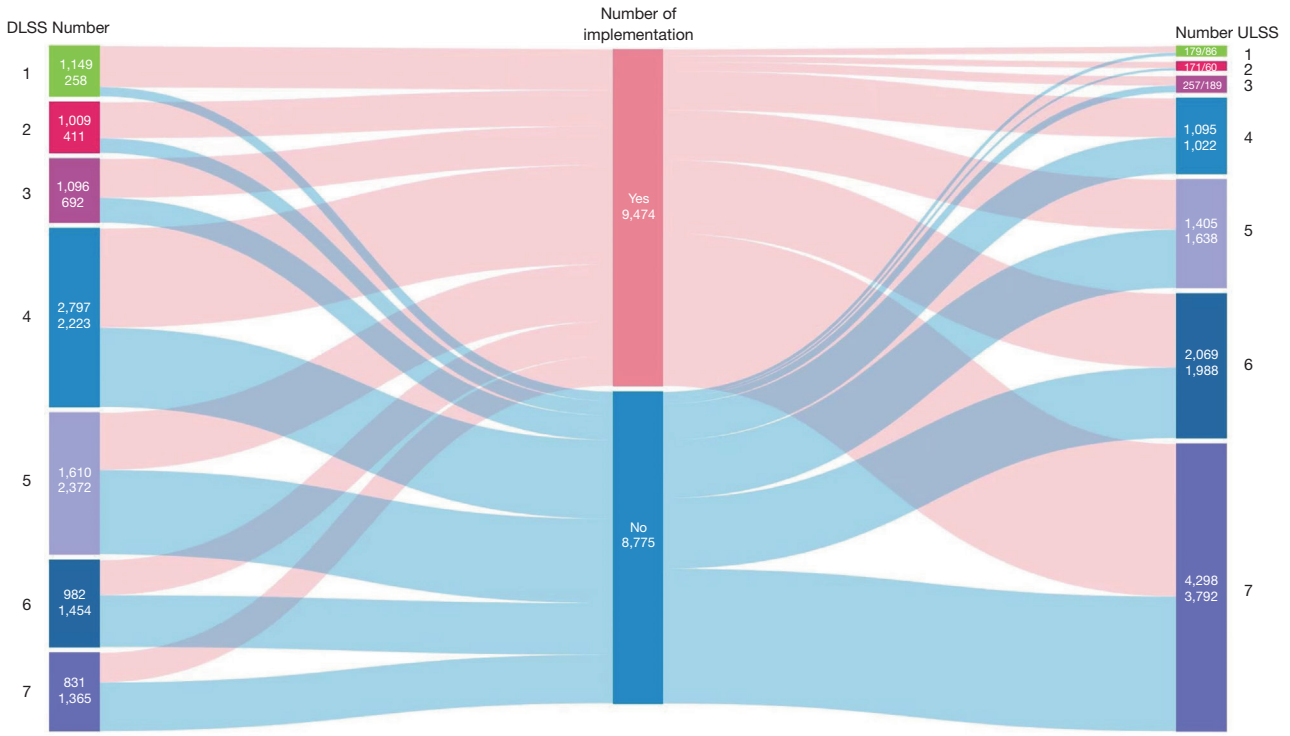

Figure 1 The association of actual recommendation implementation with the urgency and difficulty.

level is positively associated with the degree of urgency and negatively associated with the degree of difficulty of guideline implementation. Compared with secondary hospitals, for recommendations 2.5, 4.2, 6.1, 6.2, and 7.1, tertiary hospitals perceived a higher degree of urgency in guideline implementation than secondary hospitals (see Appendix 1 for the guideline recommendations). However, tertiary hospitals had lower difficulty scores of guideline implementation for recommendations 2.1, 2.2, 2.4, 2.5, 3.1, 3.2, 4.1, 5.1,7.1, and 7.3. *Table 3* details the statistically significant factors influencing the urgency and difficulty of guideline implementation.

The comments on guideline implementation

One hundred twenty-eight questionnaire respondents provided feedback or commented on implementing the Guideline. Thirty-eight respondents (29.69%) commented that the Guideline could address an important clinical issue in the current healthcare system and was eager to implement it. Twenty-five (19.53%) respondents identified barriers to the implementation of the recommendations, including the medical staff's busy schedules, the absence of off-label drugs from the medical insurance list, the national health administration's lack of leadership, and the primary medical staff's ignorance of evidence-based medicine (Table S4).

Discussion

According to this study, the recommendations in the guideline for the management of pediatric off-label use of drugs in China were implemented more in tertiary hospitals than in secondary hospitals and more in children's hospitals than in non-children's hospitals. The implementation rates of 21 recommendations ranged from 41.1% to 65.5%. The recommendations were considered less difficult for those which had put them into practice. Factors impacting the urgency and difficulty of guideline implementation were different, but the common influencing factors included the position and education level of clinicians and hospital level. The most difficult recommendation to implement was 2.3, which stated that the experts' team for the pediatric

Table 3 Multi-factor analysis of the urgency and difficulty of guideline implementation

Recommendations	The urgency of guideline implementation				The difficulty of guideline implementation			
	Factors	B	t	P	Factors	B	t	P
Theme 1. General principles and characteristics of pediatric off-label use of drugs management								
1.1 Management principles	Position	0.246	5.188	<0.001	Position	0.103	3.037	0.002
	Management experience	–0.094	–2.627	0.009				
	Work experience	–0.105	–2.271	0.023				
1.2 Refer to guidelines	Position	0.207	6.231	<0.001	Position	0.105	2.846	<0.001
					Degree	–0.088	–2.403	0.02
Theme 2. The establishment of an expert committee on the pediatric off-label use of drugs								
2.1 Expert committee	Position	0.213	6.436	<0.001	Hospital level	–0.080	–2.349	0.02
	Hospital type	–0.083	–2.506	0.012				
2.2 Co-chair	Position	0.206	6.186	<0.001	Hospital level	–0.073	–2.166	0.03
2.3 Expand experts	Position	0.146	4.351	<0.001	Position	0.074	2.192	0.03
	Hospital type	–0.089	–2.661	0.008				
2.4 Drug combination	Position	0.154	4.602	<0.001	Professional role	–0.091	–2.605	0.009
	Hospital type	–0.083	–2.478	0.013	Hospital level	–0.077	–2.224	0.03
2.5 Responsibilities and obligations	Position	0.170	4.952	<0.001	Hospital level	–0.077	–2.268	0.02
	Hospital level	0.073	2.115	0.035				
Theme 3. Evidence evaluation of off-label drug use for children								
3.1 Recommendations follow guidelines	Position	0.191	5.718	<0.001	Hospital level	–0.103	–2.957	0.003
	Hospital type	–0.068	–2.053	0.040	Position	0.086	2.482	0.01
3.2 Evaluate recommendations	Position	0.150	4.131	<0.001	Position	0.104	2.980	0.003
	Degree	0.085	2.354	0.019	Hospital level	–0.073	–2.090	0.04
Theme 4. Benefit and risk assessment of off-label drug uses in children. steps and precautions								
4.1 BRAvO decision-making framework	Position	0.174	5.032	<0.001	Position	0.197	4.067	<0.001
	Regional distribution	–0.081	–2.351	0.019	Work experience	–0.117	–2.485	0.01
					Hospital level	–0.069	–1.986	0.047
4.2 Age difference	Position	0.193	5.669	<0.001	Position	0.099	2.920	0.004
	Hospital level	0.085	2.437	0.015				
	Hospital type	–0.071	–2.111	0.035				
Theme 5. Informed consent for the off-label use of drugs in children								
5.1 Informed consent under age 8	Position	0.144	3.965	<0.001	Hospital level	–0.100	–2.910	0.004
	Degree	0.095	2.636	0.009	Hospital type	0.077	2.234	0.03
5.2 Informed consent over age 8	Position	0.080	2.177	0.030	Position	0.142	4.085	<0.001
	Degree	0.080	2.174	0.030	Degree	–0.095	–2.751	0.006

Table 3 (*continued*)

Table 3 (*continued*)

Recommendations	The urgency of guideline implementation				The difficulty of guideline implementation			
	Factors	B	t	P	Factors	B	t	P
Theme 6. Evidence-based practice for the off-label use of drugs in children								
6.1 Evidence-based medicine database	Position	0.197	5.770	<0.001	Position	0.188	4.010	<0.001
	Hospital level	0.084	2.477	0.013	Age group	–0.107	–2.292	0.002
6.2 Electronic medical record system	Position	0.185	5.414	<0.001	Position	0.184	3.918	<0.001
	Hospital level	0.093	2.734	0.006	Work experience	-0.118	-2.516	0.01
Theme 7. Monitoring and assessment of the risk of pediatric off-label use of drugs								
7.1 ADR monitor	Position	0.163	4.510	<0.001	Hospital level	–0.122	–3.513	<0.001
	Management experience	–0.080	–2.234	0.026	Position	0.100	2.870	0.004
	Hospital level	0.074	2.163	0.031				
7.2 Construct ADR monitoring system	Position	0.155	4.624	<0.001	Position	0.170	3.615	<0.001
	Hospital type	–0.077	–2.309	0.021	Work experience	–0.107	–2.275	0.02
7.3 Cooperative monitoring	Position	0.133	3.663	<0.001	Management experience	–0.100	–2.887	0.004
	Degree	0.077	2.082	0.038	Hospital level	–0.081	–2.333	0.02
	Hospital type	–0.068	–2.003	0.045				
Theme 8. Patient education on the pediatric off-label use of drugs								
8.1 Drug education	Position	0.141	3.891	<0.001	Professional role	–0.110	–3.161	0.002
	Degree	0.093	2.575	0.010	Hospital level	–0.091	–2.617	0.009
8.2 Drug information list	Position	0.155	4.302	<0.001	Hospital level	–0.087	–2.486	0.01
	Degree	0.099	2.740	0.006	Position	0.072	2.075	0.04
8.3 Popularized material	Position	0.166	4.966	<0.001	Professional role	–0.080	–2.353	0.02

off-label use of drugs should include professors who are majored in evidence-based medicine, health economics, epidemiology, ethics, and the law.

This study showed a low percentage of hospitals that had implemented the recommendations for the guideline, similar to the results of the national implementation study for the "Expert Consensus on Pediatric Off-Label Use of Drugs" (i.e., the Consensus) in 2017 (12,20). This result shows that pediatric off-label drug use management in China has been promoted slowly in the last 5 years. The consensus is yet to be well-implemented and applied after it has been produced. Similarly, healthcare professionals still need to comply more with the guidelines in Europe and the United States, where guidelines have been developed for pediatric off-label drug use (1,21,22). Numerous studies have explored barriers to implementing pediatric off-label drug use, such as financial reimbursement obstacles, a lack of familiarity with the concept of off-label drug use, and ethical and legal issues (20,21,23-26). However, more research must be done on the corresponding implementation strategies (6). Thus, it is suggested that guideline developers should design further tailored implementation strategies based on the contextual factors influencing pediatric off-label drug use.

We found that the position of healthcare professionals was the main factor impacting the degree of difficulty and urgency of the Guideline implementation. Similar to previous studies, Clinicians' position influences the implementation of guidelines (27,28). The difficulty of implementing guidelines increases with the position because pediatricians with higher position are more inclined to prescribe off-label medications (12,29-32). Based on their extensive clinical experience, amount of literature, etc., doctors with higher position are more confident in prescribing drugs off-label (31).

Hence, doctors with higher position utilize off-label drugs more frequently, making handling these common clinical practices harder. Also, the healthcare professionals with high positions believe that all recommendations should be implemented as soon as possible because healthcare professionals with high positions may be more dedicated and professional than others (33).

Common barriers to guideline implementation in health system included deficiency in staff continuous education, insufficient support from institutions, limitations of infrastructure (34). The most common barriers of healthcare professionals' failure to adhere to clinical practice guidelines aligned with the Theoretical Domains Framework (TDF) domain of environmental context and resource (35). Our study similarly found that the hospital environment impacted guidelines implementation—the hospital level and the type of hospital impacted the guideline implementation, and showed that the lower the hospital grade, the more difficult it was to implement. Presumably the low-level hospitals in China frequently need more organizational expertise and resources to follow recommendations and control off-label drug use in children (36-38). Thus, implementing the Guidelines in facilities with low-level hospitals may be more challenging than in high-level hospitals. In China, different levels of hospitals have different responsibilities, and the higher the level, the stronger the treatment capacity. Compared with higher-level hospitals, lower-level hospitals have more pressing medical resources, for example, clinicians may be less experienced in off-label drug use, hospitals may have less sophisticated management, and pharmacy departments are not equipped with rational medication use systems. Also, compared to other hospital types, healthcare professionals from children's hospitals perceived implementing guidelines as more urgent. Children's hospitals are better equipped, more refined, and better managed in pediatrics than other hospital types (39,40). Consequently, healthcare professionals from children's hospitals may feel the more urgent need for management of off-label use of drugs in children's hospitals.

As a result, we propose that several implementation strategies should be developed per various healthcare professionals position, levels of hospitals, and hospital types. Alternatively, follow the lead of China's regional medical alliances and align with children's hospitals that have already successfully implemented the recommendations, such as checking prescription system (41), prescription evaluation (41), pharmacological monitoring (42,43), and clinical pharmacy interventions (44). Resources are exchanged to enable the execution of the Guideline by sharing information across different levels of hospitals and radiating high levels of care to the grassroots, such as through medical consortia (45,46).

The investigators found that the most difficult recommendation to implement was 2.3, which stated that the experts' team for the pediatric off-label use of drugs should include professors who majored in evidence-based medicine, health economics, epidemiology, ethics, and the law. Scientific evidence is the foundation for off-label drug use, and experts in evidence-based medicine methodology can accurately assess and judge the evidence's reliability, which is indispensable in managing pediatric off-label drug use (8). Health economists can monitor and evaluate the cost of off-label use of drugs for children and optimize the use of health resources (47). Legal and ethical issues can be addressed and have long been essential factors to consider for the off-label use of drugs (48,49), especially for children (50). However, there is a large gap between clinical practice and expectations in China because Chinese hospitals usually need more experts. In China, however, there is a wide disparity between actual practice and expectations, as Chinese hospitals typically require more specialists (51-55).

Accordingly, it is suggested that national or professional organizations gather experts to develop evidence-based decision systems to respond to demands for evidence for pediatric off-label drug use, such as the German network's Pediatric Drug Information System (PDIS) (56). Additionally, to enhance the management of pediatric off-label drug use, Chinese hospital administrators are encouraged to modify the professional organization of hospitals, including the healthcare major in evidence-based medicine, health economics, epidemiology, ethics, and the law.

The questionnaire was validated by expert scale and pre-test, with questions well-designed to effectively respond to our research objectives. Our questionnaire has a good applicability and although it is not extrapolated, it can provide a reference for related studies in other countries. There are some limitations in this questionnaire. Firstly, restricted by realistic situations, the questionnaire was not distributed to primary hospitals, nor covered all the relevant professionals in the country, only sampling research was done, with limited representativeness. Secondly, there is no international common questionnaire for this research, nor could other questionnaires be adapted, this questionnaire is a self-initiated design with some limitations in question.

This study examined the current state of pediatric off-label drug use management. It demonstrated China's unsatisfactory implementation, which is part of the early-stage implementation research by the Guideline Development Working Group. The study indicates that there is a need to identify the influencing factors of the recommendations first and then tailor implementation strategies to facilitate the management of pediatric off-label use of drugs. There are some limitations in this study. Convenience sampling may lead to an unbalanced sample and affect the extrapolation of results. Our questionnaire was distributed widely and the study population is representative of China.

Conclusions

The recommendations in the Guideline for the Management of Pediatric Off-Label Use of Drugs have high urgency for implementation in China. However, the implementation of 21 recommendations was challenging in clinical practice. The key factors influencing implementation were the position, education, experience, and hospital level of healthcare professionals. We suggest implementing the recommendations by sharing experience across various hospital levels and radiating from high-level hospitals to the grassroots. Additionally, the professional structure of health care in hospitals needs to be adjusted to improve the management of off-label drug use in children.

Acknowledgments

We would like to thank Janne Estill, MD, PhD (University of Geneva) for his help in polishing our paper.
Funding: This research was funded by the Chevidence Lab Child & Adolescent Health of Chongqing Medical University's Children's Hospital's Key Project in 2022.

Footnote

Reporting Checklist: The authors have completed the SURGE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-198/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-198/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-198/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-198/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Only healthcare professionals were involved in this study without direct participation/data from children. The study was approved by the Ethics Committee of Gansu Provincial Hospital (No. 2022-152). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided informed consent to participate in the study.

References

1. Frattarelli DA, Galinkin JL, Green TP, et al. Off-label use of drugs in children. Pediatrics 2014;133:563-7.
2. Allen HC, Garbe MC, Lees J, et al. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. J Okla State Med Assoc 2018;111:776-83.
3. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. World J Pediatr 2018;14:528-40.
4. Li Y, Jia L, Teng L. A systematic review of off-label drug use at home and abroad for pediatrics. Chinese Journal of Hospital Pharmacy 2016;36:2114-9.
5. Meng M, Ge B, Lei W, et al. Paediatric off-label use of drugs in Gansu, China: a multicentre cross-sectional study. BMJ Open 2024;14:e078126.
6. Meng M, Lv M, Wang L, et al. Off-label use of drugs in pediatrics: a scoping review. Eur J Pediatr 2022;181:3259-69.
7. Wu Y. The expert consensus on off-label drugs in pediatrics in China. Chinese Journal of Pediatrics 2016;54:101-3.

8. Meng M, Liu E, Zhang B, et al. Guideline for the management of pediatric off-label use of drugs in China (2021). BMC Pediatr 2022;22:442.
9. Chen Y, Shi Q, Zhao J, et al. From Knowledge to Action:Bridging the Gap Between Theory and Practice in Clinical Practice Guidelines. Medical Journal of Peking Union Medical College Hospital 2020;11:746-53.
10. Ma X, Zhao L, Ma L, et al. Current status of popularization and application of relevant guidelines for diabetes prevention and treatment in China at grass-roots level. Journal of Community Medicine 2019;17:1167-70.
11. Liu M, Zhang C, Zha Q, et al. A national survey of Chinese medicine doctors and clinical practice guidelines in China. BMC Complement Altern Med 2017;17:451.
12. Mei M, Wang L, Liu E, et al. Current practice, management and awareness of pediatric off-label drug use in China-A questionnaire based cross-sectional survey. Chinese Journal of Evidence Based Pediatrics 2017;12:289-94.
13. Bierbaum M, Rapport F, Arnolda G, et al. Clinicians' attitudes and perceived barriers and facilitators to cancer treatment clinical practice guideline adherence: a systematic review of qualitative and quantitative literature. Implement Sci 2020;15:39.
14. Nyanchoka L, Tudur-Smith C, Porcher R, et al. Key stakeholders' perspectives and experiences with defining, identifying and displaying gaps in health research: a qualitative study. BMJ Open 2020;10:e039932.
15. Wang Q, Wang X, Chen Y, et al. Research gap of guidelines might be an important approach to prioritization (Letter commenting on: J Clin Epidemiol. 2015;68:341-6). J Clin Epidemiol 2016;69:251-2.
16. Fischer F, Lange K, Klose K, et al. Barriers and Strategies in Guideline Implementation-A Scoping Review. Healthcare (Basel) 2016;4:36.
17. Meng M, Hu J, Liu X, et al. Barriers and facilitators to guideline for the management of pediatric off-label use of drugs in China: a qualitative descriptive study. BMC Health Serv Res 2024;24:435.
18. Otto E, Culakova E, Meng S, et al. Overview of Sankey flow diagrams: Focusing on symptom trajectories in older adults with advanced cancer. J Geriatr Oncol 2022;13:742-6.
19. Lamer A, Laurent G, Pelayo S, et al. Exploring Patient Path Through Sankey Diagram: A Proof of Concept. Stud Health Technol Inform 2020;270:218-22.
20. Mei M, Xu H, Wang L, et al. Current practice and awareness of pediatric off-label drug use in Shanghai, China -a questionnaire-based study. BMC Pediatr 2019;19:281.
21. Balan S, Hassali MA, Mak VS. Awareness, knowledge and views of off-label prescribing in children: a systematic review. Br J Clin Pharmacol 2015;80:1269-80.
22. Schrier L, Hadjipanayis A, Stiris T, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr 2020;179:839-47.
23. deSante-Bertkau JE, Knilans TK, Persad G, et al. Off-Label Prescription of COVID-19 Vaccines in Children: Clinical, Ethical, and Legal Issues. Pediatrics 2022;149:e2021054578.
24. Balan S, Ahmad Hassali MA, Mak VSL. Attitudes, knowledge and views on off-label prescribing in children among healthcare professionals in Malaysia. Int J Clin Pharm 2019;41:1074-84.
25. AbuAlsaud Z, Alshayban D, Joseph R, et al. Off-label Medications Use in the Eastern Province of Saudi Arabia: The Views of General Practitioners, Pediatricians, and Other Specialists. Hosp Pharm 2020;55:37-43.
26. Piñeiro Pérez R, Ruiz Antorán MB, Avendaño Solá C, et al. Results from the 2012-2013 paediatric national survey on off-label drug use in children in Spain (OL-PED study). An Pediatr (Barc) 2014;81:16-21.
27. Zeng L, Li Y, Zhang L, et al. Guideline use behaviours and needs of primary care practitioners in China: a cross-sectional survey. BMJ Open 2017;7:e015379.
28. Shingching T, Chunqiong D, Dany T, et al. A survey of ophthalmologists ' cognition and application of clinical guidelines. Chinese Clinical Medicine 2018;25:972-6.
29. Xu J, Liu Y, Zhang H. Current situation and analysis of off-label drug use in pediatric outpatient department of a hospital. Proceeding of Clinical Medicine 2021;30:371-4.
30. Zhu M, Zhu H, Chen C. Investigation of Off-Label Drug Use in Pediatrics of a Hospital in 2017. Journal of Pediatric Pharmacy 2020;26:42-4.
31. U F, Wen Y, Chen W, et al. Multicenter Study Off-lable Drug Use Analysis of Psychotropic Medication in Children and Adolescent Psychiatric Patients. Pharmacy Today 2017;27:706-9.
32. Tang W, Zhang S, Zhou W, et al. A cross-sectional survey on drug use exceeded specification of children's respiratory wards in single center. Chinese Journal of Evidence-Based Pediatrics 2017;12:33-7.
33. Wu C, Wang Y. Multi-dimensional perspective and enlightenment on cognitive differences of medical

workers' professional accomplishment. Health Vocational Education 2019;37:131-5.
34. Correa VC, Lugo-Agudelo LH, Aguirre-Acevedo DC, et al. Individual, health system, and contextual barriers and facilitators for the implementation of clinical practice guidelines: a systematic metareview. Health Res Policy Syst 2020;18:74.
35. Stewart D, Al Hail M, Al-Shaibi S, et al. A scoping review of theories used to investigate clinician adherence to clinical practice guidelines. Int J Clin Pharm 2023;45:52-63.
36. Li T, Liu Z, Yang H, et al. Investigation and analysis of the implementation status of "Diagnosis and therapy guideline of preterm birth (2014)". Chinese Journal of Obstetrics and Gynecology 2022;57:449-55.
37. Jia C, Liu B, Li X, et al. Effect of Anluo Huaxian Pill Combined with Entecavir on Viral Replication, Liver Fibrosis Markers and Th1/Th2 Cytokines in Patients with Chronic Hepatitis B Virus Infection. Journal of Liaoning University of Traditional Chinese Medicine 2017;19:146-9.
38. Wu C, Xie G. Differences in perceived professionalism of medical workers in different levels of hospitals and insights. Medical Management 2018:184-6.
39. Zhang X, Luo Y, Mo C, et al. Comparative Analysis of Pediatric Medical Service Capacity Based on DRGs in Sichuan Province. Chinese Health Quality Management 2020;27:51-4.
40. Gao S, Tao Y, Chen Y, et al. Construction Measures of Pediatric Disciplines of a Comprehensive Hospital. Hospital Administration Journal of Chinese People's Liberation Army 2017;24:629-31+36.
41. Zhang Q, Shi X, Li Z. Practice and Analysis of Regulation for Pediatric Prescriptions/Medical Orders Pre-Review System. Journal of Pediatric Pharmacy 2021;27:18-21.
42. Yang D, He J, Chai L, et al. Pharmaceutical care for the treatment using oxycodone hydrochloride sustainedrelease tablets by rectal administration in children with cancer pain by clinical pharmacists. Journal of Modern Oncology 2018;26:1266-9.
43. Chen Z, Ye Y, Shen Y, et al. Pharmaceutical care of an outpatient child for off-label use of hydroxychloroquine. Shanghai Medical & Pharmaceutical Journal 2020;41:69-71.
44. Lin X, Ye J, Zhang H, et al. Effectiveness analysis of clinical pharmacists intervening in off-abel drug use in hospitalized children. Chinese Journal of Clinical Pharmacy 2018;27:354-7.
45. Langlois EV, Becerril Montekio V, Young T, et al. Enhancing evidence informed policymaking in complex health systems: lessons from multi-site collaborative approaches. Health Res Policy Syst 2016;14:20.
46. Liang J, Zheng X, Chen Z, et al. The experience and challenges of healthcare-reform-driven medical consortia and Regional Health Information Technologies in China: A longitudinal study. Int J Med Inform 2019;131:103954.
47. Blankart KE, Lichtenberg FR. The effects of off-label drug use on disability and medical expenditure. National Bureau of Economic Research 2022.
48. Lenk C, Duttge G. Ethical and legal framework and regulation for off-label use: European perspective. Ther Clin Risk Manag 2014;10:537-46.
49. Bell JS, Richards GC. Off-label medicine use: Ethics, practice and future directions. Aust J Gen Pract 2021;50:329-31.
50. Kölch M, Allroggen M, Fegert JM. Off-label use in child and adolescent psychiatry. An ongoing ethical, medical and legal problem. Nervenarzt 2009;80:789-96.
51. Wu L, Liu G, Shi Y, et al. Ethical Practice of Off-Label Drug Use in Children. Evaluation and Analysis of Drug-Use in Hospitals of China 2020;20:734-7,41.
52. Fan J, Zhang W, Su J, et al. Problems and Countermeasures in Construction of Ethics Committee in Grass roots Hospitals. Medicine & Philosophy 2020;41:29-31.
53. Hu S, Yu Y. Practice and Thoughts on the Rule of Law Construction of Public Hospitals under the Background of Medical System Reform. Shanghai Management Science 2022;44:116-9.
54. Sharma AN, Arango C, Coghill D, et al. BAP Position Statement: Off-label prescribing of psychotropic medication to children and adolescents. J Psychopharmacol 2016;30:416-21.
55. Lin S, Qi Q, Liu Z, et al. Effect of Entecavir Combined with Biejiajian Pill in the Treatment of Chronic Viral Hepatitis B. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine 2021;31:60-2.
56. Zahn J, Wimmer S, Rödle W, et al. Development and Evaluation of a Web-Based Paediatric Drug Information System for Germany. Pharmacy (Basel) 2021;9:8.

Cite this article as: Meng M, Hu J, Lei W, Tian M, Liu X, Lu Y, Liu E, Zhang S, Han Z, Li Q, Chen Y. The implementation of the guideline for the management of pediatric off-label use of drugs in China: a cross-sectional study. Transl Pediatr 2024;13(8):1425-1438. doi: 10.21037/tp-24-198